

Synthesis and Identification of Some 8-Hydroxy Quinoline Derivatives and Study of its Biological Activity as an Antibacterial

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ABSTRACT

This study includes the synthesis of some derivatives of 8-hydroxy quinoline from react (2-amino-6-methoxy benzothiazole) With (8-hydroxy quinoline) to give Azo derivative (1) that react with Ethyl bromo acetate to give ester derivative (2). Then (2) compound will react with Hydrazine hydrate to give hydrazine derivative (3). Then (3) will react with (PhSCN) to yelred (4), (3) react with ethyl acetoacetate to give (5). Then (5) react with 10% sodium hydroxide to give (6), (3) react with acetyl acetone to yelred pyrazol derivative (7), (3) React with ammonium thiocyanate to give (8), then (8) react with sodium hydroxide 10% to give thiazine derivative (9), (4) React with sulfuric acid and sodium hydroxide to give (10) and (11) respectively. All these compounds are characterized by Fourier transforms infrared spectroscopy (FT-IR), (HNMR), after that we study biological activity for all compounds derivatives.

Keywords: Hetero cyclic compounds, Thiazole, triazole

1. Introduction

Heterocyclic compounds (like carbocyclic compounds) can be divided in to aromatic and un aromatic heterobicyclic [1-3]. These compounds are of great importance and are widespread in nature, for example sugars and their derivatives and vitamins such as vitamin C, which is found in the form of a five-ring (Furan) and vitamin B6 containing pyridoxine and alkaloids [4, 5].Thiazole have a typical formula of (C₃H₃NS) and are organic five-aromatic ring compounds [6]. Free thiazole is a light yellow liquid with a pyridine-like odor[7].The following are examples of thiazole resonating structures. Nonetheless, some resonant assemblages involving sulfur d-orbitals are also feasible[8].The structure of vitamin B (thiamine) includes the thiazole nucleus [9], Sulfathiazole, aztreonam, and a variety of cepheims (ceftaroline, cefotiam, ceftibuten, cefixime, ceftriaxone, cefotaxime, ceftazidime, cefmenoxime, ceftizoxime, cefpime, cefdinir) with antibacterial properties; pramipexole with antiparkinsonian disease [10, 11].Thiazole, or 1,3-thiazole, belongs to the class of azoles and contains one sulfur atom and one nitrogen automat positions 1 and 3. Its diverse biological activity is reflected in a large number of clinically approved thiazole-containing compounds with an extensive range of pharmacological activities[12].Thiazole are present in numerous natural products e.g. epithilone, thiostrepton, thiamine pyrophosphate (TPP),carboxylase vitamin B1, and penicillin.Thiazole have diverse applications in drug development for treatment allergies,inflammation,HIV infections,hypertension,bacterial infections,hypnotics, Schizophrenia,and pain,as novel inhibitors of bacterial DNA gyrase B10[13].The copper-catalyzed synthesis of triazole derivatives has gained a great amount of attention because of diversity in pharmacological activities, medicinal chemistry,materials science, and

chemical biology[14].Antimicrobial resistance (AMR) has been a worldwide concern that became a never-ending fight between humans and the micro biome. Microbial infections are estimated to cause 0.7 million deaths annually and increasing on an everyday basis[15].

2. Material

(FTIR) Spectra (400 -4000 cm⁻¹) in KBr disk were recorded on SHIMADZU FTIR-8400S Fourier transform. 13C-NMR and 1HNMR were recorded on Varian Agilent USA at (500MHz) with (DMSO-d₆) measurements were made at Department of Chemistry, Education college, University of Basra.

Preparation of compound (1)[16].

Different mole were mixed from (0.0053 mol, 1.8 g) of the compound (2-amino-6-methoxy benzo thiazole) dissolve in (60 ml) distilled water with (4 N, 4 ml) of hydrochloric acid in (0-50) Co to get diazonium salt then added (0.7 g, 0.01 mol) sodium nitrate dissolved in (20 ml) of distilled water, next we added the whole mixture to (1.45 g, 0.01mol) of (8-hydroxy quinoline) also dissolved in distilled water, we put the mixture on the sterol at (PH= 5) for (2 hours) in ice path (0-5)Co after that we flittered the solution with purple color precipitate, 336.73 g/mol the molecular weight, the percentage is 63%, melting point is 132 Co, Rf = 0.37.

Preparation of compound [17].

(0.99 g, 0.0029 mol) of compound (A1) with (0.33 ml) of ethyl bromo acetate and (1.035 g) from potassium carbonate anhydrate were dissolved in (100 ml) of acetone then the whole mixture refluxed for (24 hours), the reaction was followed by TLC technique. the precipitate was filtered and then recrystallization by absolute ethanol, the color dark brawn, molecular weight 422.46 g/mol, percentage 70 %, melting point 137 Co, Rf = 0.42.

Preparation of compound (3)[18]

(2 g, 0.004 mol) were taken from the compound (A2) and mixed with (15 ml) hydrazine hydrate in (25ml) of Absolute ethanol, the solution were refluxed for (3 hours) in temperature (80 Co) the reaction was followed by TLC technique, the precipitate was filtered and then recrystallization by absolute ethanol, the color yellow, molecular weight 408.44 g/mol, percentage 72 %, melting point 108 Co, Rf = 0.42.

Preparation of compound(4)[19]

(4 g, 0.01 mol) of hydrazine derivative (A3) was mixed with (1.206 ml,0.01 mol) of (PhNCN) compound in (25 ml) of absolute ethanol solvent using water bath (70 Co) for (5 hours) with follow-up interaction with the technique of kromotokravia thin layer TLC, then cool to form deposit and filter, recolor and dry by methanol.the solution with brown color, 556.11 g/mol the molecular weight, the percentage is 77%, melting point is 90 Co, Rf = 0.37.

Preparation of compound 2 (5)[20]

Blended (2 g, 0.00489 mol) of derivative (3) with (1.2758 ml, 0.01 mol) of the compound Ethyl aceto acetate in (10 ml) of Acetic acid. the mixture was reflexed for (5 hours) the mixture cooled and poured on ice distilled water and then recrystallized by absolute ethanol.the solution with black color, 474.50 g/mol the molecular weight, the percentage is 79%, melting point is 152 Co, Rf = 0.40.

Preparation of compound(6)[21]

(0.5046 g, 0.01 mol) of derivative (A5) was dissolved in (10%) of the compound Sodium hydroxide, heated by escalation for (6 hours) and continues to interact with TLC technology The solution is then poured on iced water and is equivalent with a diluted solution of Hydrochloric acid and then filtered and recrystallized by absolute ethanol. the solution with black color, 506.14 g/mol the molecular weight, the percentage is 81%, melting point is 119 Co, Rf = 0.37.

Preparation of compound(7)[22]

(2 g, 0.00489 mol) of derivative (A3) was mixed with (1.0217 ml) of compound Acetyl acetone in (10 ml) of Acetic acid the escalation was carried out for (9 hours) and follow-up interaction with the technique of the thin layer Kromotokravia TLC, after which poured the mixture in ice water and then collected the solid output and was re-crystallized by absolute ethanol, the solution with black color, 458.50 g/mol the molecular weight, the percentage is 82%, melting point is 122 Co, Rf = 0.52.

Preparation of compound(8)[23]

(4.9352 g, 0.01 mol) of derivative (A3) with (0.7601 g, 0.01 mol) of the dissolved compound Ammonium thiocyanate in (0.7601 g, 0.01 mol) in (20 ml) Absolute ethanol was escalated for (9 hours) and follow-up interaction with TLC technology and then left for (24 hours) and filtered and re-crystallized with ethanol, the solution with black color, 493.52 g/mol the molecular weight, the percentage is 81%, melting point is 90 Co, Rf = 0.54.

Preparation of compound(9)[24]

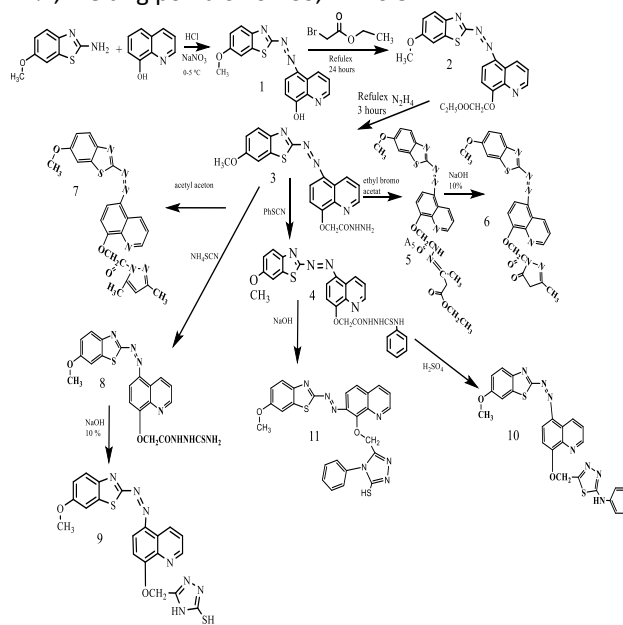
(1.11222 g, 0.002 mol) from the dissolved derivative (A4) in (20 ml) of Absolut ethanol mixed with (4 N, 2ml) of Sodium hydroxide and escalated for (2 hours) and followed up with technology TLC is treated with charcoal coal carbon and then filters, the result has been cooled and the PH equation (4-6) by Glacial acetic acid diluted, leaving the output for an hour and then filtered, dried, re-crystallized with ethanol, the solution with black color, 540.12 g/mol the molecular weight, the percentage is 82%,melting point is 83 Co, Rf = 0.49.

Preparation of compound (10)[25]

(1 g) of the derivative compound (B5) was escalated in 5 % of Sodium carbonate (10 ml) for (5 hours) and the interaction was followed up with the technique of kromocaravia thin layer TLC and then roasted by hydrochloric acid diluted, deposited and re-crystallized with ethanol, the solution with black color, 449.07 g/mol the molecular weight, the percentage is 78%, melting point is 113 Co, Rf = 0.41.

Preparation of compound(11)[26]

(1.1222 g, 0.002 mol) from derivative (A4) added to (5 ml) of sulfuric acid concentrated, the mixture left for (2 hours), after that the products thrown on crushed ice of distilled water and the solid output was filtered and washed with distilled water and dried and re-crystallized with absolute ethanol, the solution with black color, 527.62 g/mol the molecular weight, the percentage is 74%, melting point is 101 Co, Rf = 0.51.



Scheme (1): synthesis of 1-11 compounds

3. Results and Discussion

Characterization of the compound (1)

5-((6-methoxybenzothiazole-2-yl) diazenyl) quinolin-8-ol FT-IR spectrum data for the derivative (1) show absorption packs at (3433- 3440 cm⁻¹) for OH, and N-H overlapping, 3055 cm⁻¹ for (Ar-H), 2931 cm⁻¹ for (C-H) in CH₃, 1419 cm⁻¹ for (N=N), 1226 cm⁻¹ for (C-O) aromatic. ¹HMR Spectrum data of compound (1) show 3.8ppm (S, 3H,(OCH₃)), 9.08ppm (S,1H,OH), 6.7-8.8ppm

(M,8H,Ar-H).¹³C-NMR Spectrum data of compound (1) show 174ppm (C1), 173ppm (C11), 170ppm (C3), 158ppm (C12), 152ppm (C6), 149ppm (C7), 145ppm (C16), 125ppm (C8), 56ppm (C17), 104-123 ppm (CArom).

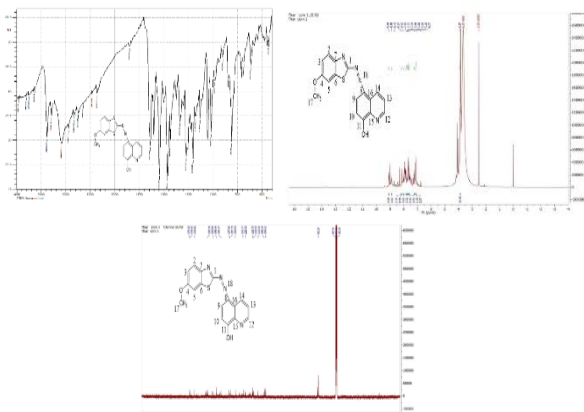


Fig. (1): FTIR, H-NMR and ¹³C-NMR spectra of compound (1)

Characterization of the compound (2)

Ethyl-2-((5-((6-methoxy benzothiazol-2-yl)diazenyl) quinoline-8-yl)oxy) acetate

FT-IR spectrum date for the derivative (2) show absorption packs at (1680 cm⁻¹) for C=O, 3078 cm⁻¹ for (Ar-H), 2947 cm⁻¹ for (C-H) in CH₃, 1473 cm⁻¹ for (N=N), 1226 cm⁻¹ for (C-O) aromatic. ¹HMR Spectrum data of compound (2) show 3.8ppm (S, 3H, (OCH₃)), 3.87ppm (S, 2H, (CH₂)), 1.3ppm (t, 3H, (CH₃)), 2.09ppm (q, 2H, (CH₂)), 6.5-8.6ppm (M, 8H, Ar-H).

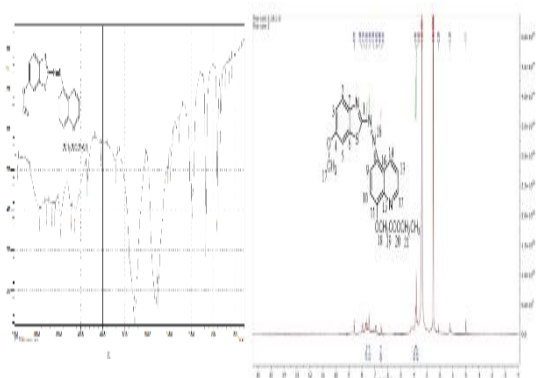


Fig. (2): FTIR and H-NMR spectra of compound (2)

Characterization of the compound (3)

2-((5-((6-methoxybenzo[d]thiazol-2-yl)diazenyl) quinolin-8-yl)oxy)acetohydrazide

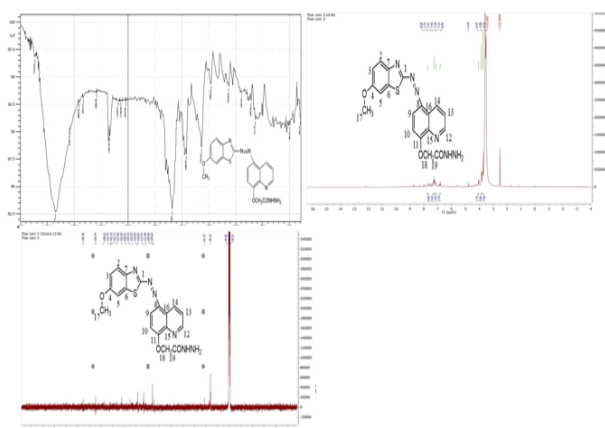


Fig. (3): FTIR, H-NMR and ¹³C-NMR spectra of compound (3)

FT-IR spectrum date for the derivative (3) show absorption packs at (3310- 3390 cm⁻¹) for NH, NH₂ 3078 cm⁻¹ for (Ar-H), 2908 cm⁻¹ for (C-H) in CH₃, 1458 cm⁻¹ for (N=N), 1226 cm⁻¹ for (C-O) aromatic. ¹HMR Spectrum data of compound (3) show 3.86ppm (S, 3H, (OCH₃)), 3.7ppm (S, 2H, (CH₂)), 4.07ppm (S, 2H, (NH₂)), 4.7ppm (S, H, (NH)), 6.3-8ppm (M, 8H, Ar-H). ¹³C-NMR Spectrum data of compound (3) show 165ppm (C19), 154ppm (C1), 61ppm (C17), 56ppm (C18), 148ppm (C11), 143ppm (C3), 142ppm (C12), 141ppm (C6), 104-137ppm (CArom).

Characterization of the compound (4)
2-(2-((5-((6-methoxybenzothiazol-2-yl) diazenyl) quinoline-8-yl) oxy) acetyl-N-phenyl hydrazine-carbothioamide

FT-IR spectrum date for the derivative (4) show absorption packs at 3434 cm⁻¹ for (N-H) overlapping, 2923 cm⁻¹ for (C-H), 2337 cm⁻¹ for (C-N), 1419 cm⁻¹ for (N=N), 1226 cm⁻¹ for (C-O) aromatic 1630 cm⁻¹ for (C=C). ¹HMR Spectrum data of compound (4) show 4.07-5.02 ppm (S, 3H, (NH)), 3.7 ppm (S, 2H, (CH₂)), 3.9 ppm (S, 3H, (OCH₃)), 6.5-8.2 ppm (M, 7H, Ar-H). ¹³C-NMR Spectrum data of compound (4) show 176 ppm (C19), 164 ppm (C20), 5.9 ppm (C18), 54.1ppm (C17), 155 ppm (C1), 146 ppm (C6, C7), 104-140ppm (CArom).

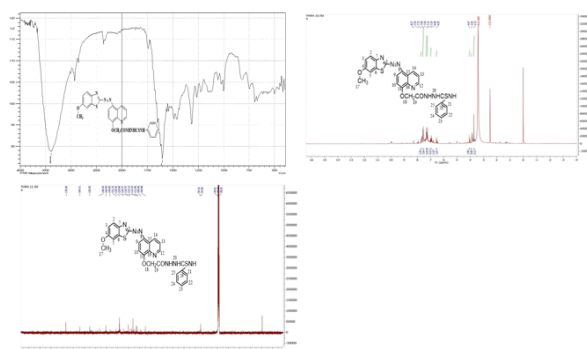


Fig. (4): FTIR, H-NMR and ¹³C-NMR spectra of compound (4)

Characterization of the compound (5)

Ethyl(3E)-3-(2-(2-((5-((6-methoxybenzothiazol-2-yl) diazenyl) quinolin-8-yl) oxy) acetyl) hydrazineylidene) butanoate

FT-IR spectrum date for the derivative (5) show absorption packs at 3332- cm⁻¹ for N-H, 3224cm⁻¹ For (=C-H), 2939 cm⁻¹ for (C-H), 1434 cm⁻¹ for (N=N), 1630 cm⁻¹ for (C=O), 1226 cm⁻¹ for (C-O) aromatic. ¹HMR Spectrum data of compound (5) show 4.09 ppm (S, 1H, (NH)), 3.7 ppm (S, 3H, (OCH₃)), 1.2 ppm (S, 3H, (CH₃)), 2.1 ppm (S, 2H, (CH₂)), 7.1-8.2 ppm (M, 8H, Ar-H), 2.2 ppm (t, 3H, (CH₃)), 3.8 ppm (q, 2H, (CH₂)).

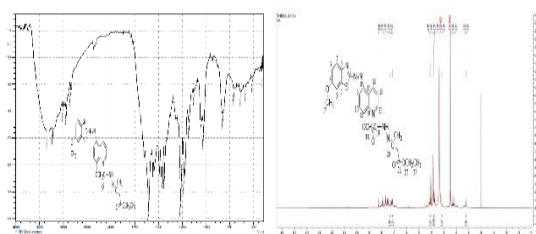


Fig (5): FTIR and H-NMR spectra of compound (5)

Characterization of the compound (6)

2-(2-((5-((6-methoxybenzothiazol-2-yl) diazenyl) quinoline-8-yl) oxy) acetyl)-5-methyl-2,4-dihydro-3H-pyrazol-3-one

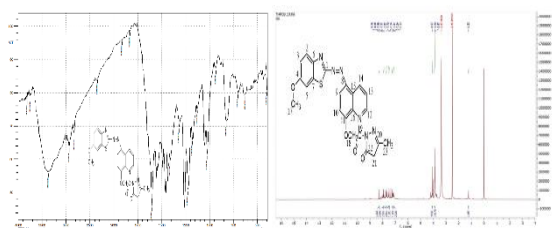


Fig. (6): FTIR and H-NMR spectra of compound (6)

FT-IR spectrum data for the derivative (6) show absorption peaks at 3363 cm⁻¹ for (N-H), 2931 cm⁻¹ for (C-H), 1566 cm⁻¹ for (C=O), 1411 cm⁻¹ for (N=N), 1226 cm⁻¹ for (C-O) aromatic. ¹H-NMR Spectrum data of compound (6) show 1.2 ppm (S, 3H, CH₃), 3.8 ppm for (S, 3H, OCH₃), 4.0 ppm for (S, 2H, CH₂=O), 3.9 ppm for (S, 2H, CH-O).

Characterization of the compound (7)

(Z)-1-(3,5-dimethyl-1H-pyrazol-1-yl)-2-((5-6-methoxybenzothiazol-2-yl) diazenyl) quinoline-8-yl) oxy) ethan-1-one

FT-IR spectrum data for the derivative (7) show absorption peaks at 3317 cm⁻¹ for (N-H), 2939 cm⁻¹ for (C-H), 2337 cm⁻¹ for (C-N), 1434 cm⁻¹ for (N=N), 1226 cm⁻¹ for (C-O) aromatic. ¹H-NMR Spectrum data of compound (7) show 1.2 ppm (S, 6H, CH₃), 4.0 ppm (S, 3H, OCH₃), 3.8 ppm (S, 2H, CH₂), 7.1-8.2 ppm (M, 9H, Ar-H).

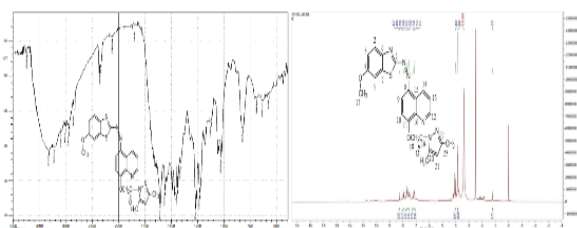


Fig. (7): FTIR and H-NMR spectra of compound (7)

Characterization of the compound (8)

(Z)-2-((5-((6-methoxybenzothiazol-2-yl) diazenyl) quinoline-8-yl) oxy) acetyl) hydrazine-1-Carbothioyl azide
FT-IR spectrum data for the derivative (8) show absorption peaks at 3494 cm⁻¹ for (N-H), 2831 cm⁻¹ for (C-H), 2337 cm⁻¹ for (C-N), 1404 cm⁻¹ for (N=N), 1226 cm⁻¹ for (C-O) aromatic. ¹H-NMR Spectrum data of compound (8) show 3.7 ppm (S, 3H, OCH₃), 1.9 ppm (S, 2H, CH₂), 4.08 ppm (S, H, C=O), 3.87 ppm (S, 1H, NH-C=O), 4.9 ppm (S, 2H, NH₂), 6.6-8.2 ppm (M, 8H, Ar-H). ¹³C-NMR Spectrum data of compound (8) show 56 ppm (C₁₇), 57 ppm (C₁₈), 165 ppm (C₁₉), 156 ppm (C₁), 154 ppm (C₂₀), 106-142 ppm (CArom), 146 ppm (C₆ - C₇).

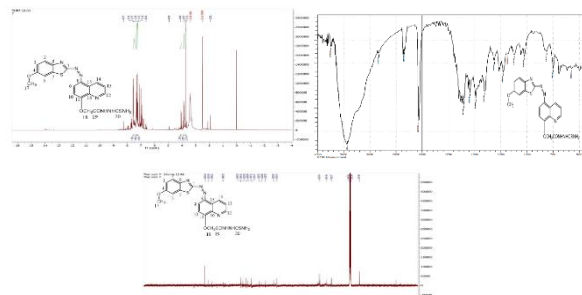


Fig. (8): FTIR, H-NMR and ¹³C-NMR spectra of compound (8)

Characterization of the compound (9)

(E)-5-(((7-((6-methoxybenzothiazol-2-yl) diazenyl) quinoline-8-yl) oxy) methyl)-4-phenyl-4,5-dihydro-1,2,4-triazine-3-thiol

FT-IR spectrum data for the derivative (9) show absorption peaks at 3363-3379 cm⁻¹ for (N-H), 2977 cm⁻¹ for (C-H), 2337 cm⁻¹ for (C-N), 1419 cm⁻¹ for (N=N), 1257 cm⁻¹ for (C-O). ¹H-NMR Spectrum data of compound (9) show 3.87 ppm (S, 3H, OCH₃), 4.48 ppm (S, 1H, SH), 1.85 ppm (S, 2H, CH₂), 6.8-8.6 ppm (M, 8H, Ar-H). ¹³C-NMR Spectrum data of compound (9) show 56 ppm (C₁₇), 56.1 ppm (C₁₈), 156 ppm (C₁), 154 ppm (C₂₀), 147 ppm (C₆-C₇), 142 ppm (C₁₆-C₁₅), 105-141 ppm (CArom).

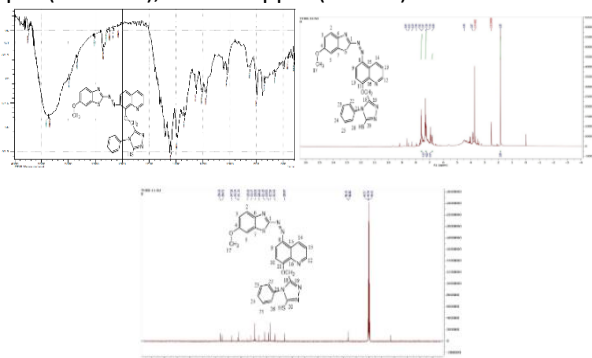


Fig. (9): FTIR, H-NMR and ¹³C-NMR spectra of compound (9)

Characterization of the compound (10)

(Z)-3-(((5-((6-methoxybenzothiazol-2-yl) diazenyl) quinoline-8-yl) oxy) methyl)-3H-1,2,4-triazol-5-thiol

FT-IR spectrum data for the derivative (10) show absorption peaks at 3371 cm⁻¹ for (N-H), 2931 cm⁻¹ for (C-H), 2337 cm⁻¹ for (C-N), 1411 cm⁻¹ for (N=N), 1226 cm⁻¹ for (C-O) aromatic. ¹H-NMR Spectrum data of compound (10) show 9.8 ppm (S, 1H, NH), 4.45 ppm (S, 1H, SH), 3.78 ppm (S, 3H, OCH₃), 3.38 ppm (S, 2H, CH₂), 6.7-8.2 ppm (M, 8H, Ar-H). ¹³C-NMR Spectrum data of compound (10) show 55 ppm (C₁₈), 58 ppm (C₁₇), 156 ppm (C₁), 154 ppm (C₂₀), 147 ppm (C₆-C₇), 104-141 ppm (CArom).

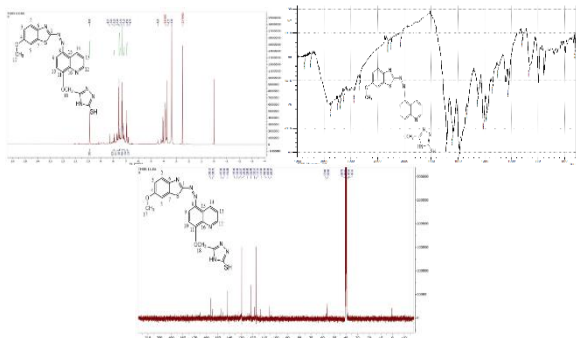


Fig. (10): FTIR, H-NMR and ¹³C-NMR spectra of compound (10)

Characterization of the compound (11)

(Z)-5-(((5-((6-methoxybenzothiazol-2-yl) diazenyl) quinoline-8-yl)oxy)methyl)-N-phenyl-2,5-dihydro-1,3,4-thiazol-2-amine

FT-IR spectrum data for the derivative (11) show absorption peaks at 3438 cm⁻¹ for (N-H), 2831 cm⁻¹ for (C-H), 2337 cm⁻¹ for (C-N), 1488 cm⁻¹ for (N=N), 1265 cm⁻¹ for (C-O) aromatic. ¹H-NMR Spectrum data of compound (11) show 4.4 ppm (S,1H,NH), 4.0 ppm (S,3H,OCH₃), 3.7 ppm (S,2H,CH₂), 3.38 ppm, 6.9-8.7 ppm (M,13H,Ar-H). ¹³C-NMR Spectrum data of compound (A11) show 57 ppm (C17), 56 ppm (C18), 156 ppm (C1), 154 ppm (C20), 104-134 ppm (CArom).

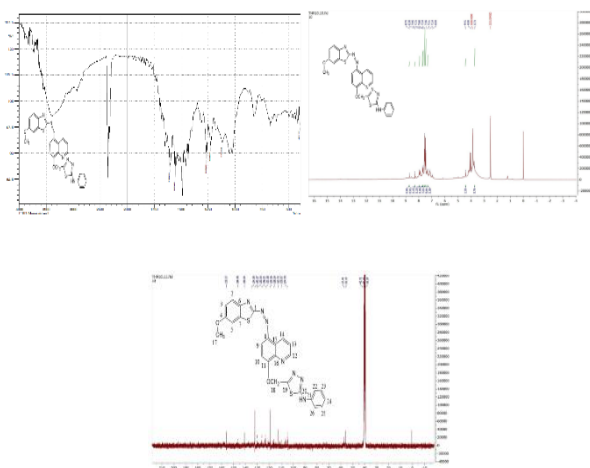


Fig. (11): FTIR, H-NMR and ¹³C-NMR spectra of compound (11)

4. Biological activity

The biological efficacy of all compounds prepared in this study was studied, with two types of pathological bacteria prepared in the laboratory and two types of bacteria, one positive for Staphylococcus aureus and a gram-negative bacterium for Escherichia coli. The results of the antibacterial activity are shown in the fig (22)

mm	S.aureus	mm	E.Coli	No. of comp.
1.5	+++	0.1	++	1
0.1	++	1.6	++	2
0.1	++	0.2	+	3
0.7	++	0.4	++	4
0.2	+	0.5	++	5

1.5	+++	0.1	++	6
0.1	++	0.2	++	7
0.7	+++	0.1	+++	8

+= (0-0.3)mm = slightly active, ++ = (0.4-0.9)mm moderately, +++ = More than 0.9 mm, good active

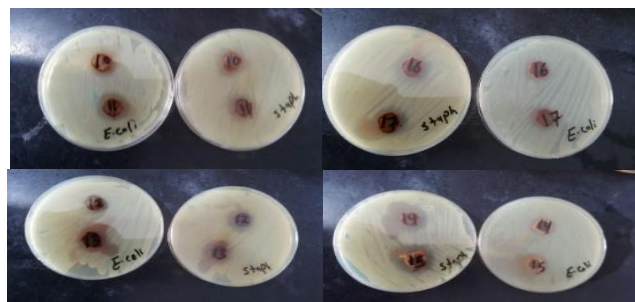


Fig (12) effect compounds (E.Coli) against (S.aureus)

Yield %	Color	Rf	M.p (°C)	M.W	M.F	Comp.
77	Brown	0.37	90	556.11	C ₂₆ H ₂₁ N ₇ O ₃ S ₂	1
79	Black	0.40	152	520.56	C ₂₅ H ₂₄ N ₆ O ₅ S	2
81	Black	0.37	119	474.50	C ₁₉ H ₁₆ N ₆ O ₃ S	3
82	Black	0.52	122	472.52	C ₂₄ H ₂₀ N ₆ O ₃ S	4
81	Black	0.54	90	493.52	C ₂₀ H ₁₅ N ₉ O ₃ S ₂	5
82	Black	0.49	83	539.63	C ₂₇ H ₂₁ N ₇ O ₂ S ₂	6
78	Black	0.41	113	449.51	C ₂₀ H ₁₅ N ₇ O ₂ S ₂	7
74	Black	0.51	101	527.62	C ₂₆ H ₂₁ N ₇ O ₂ S ₂	8

5. Conclusion

This research relied on the prepared some 8-hydroxy quinoline derivatives, which mainly led to the diagnosis of the compounds prepared on several techniques thereof (FT-IR, ¹H-NMR) and their evaluation against two types of bacteria these compounds were stable and have good biological efficacy.

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